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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,683	06/24/1999	GREGOR CEVC	35946-701.831	2670

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/284,683	CEVC, GREGOR	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106,112-115,118,120-124 and 129-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106,112-115,118,120-124 and 129-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-24-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 3-24-09 is acknowledged.

Claims included in the prosecution are 106, 112-115, 118 and 120-124 and 129-138.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 106, 112-115, 118 and 120-124 and 129-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Instant claims recite 'consisting essentially of' with further limitations of 'salt of one ore more non-steroidal anti-inflammatory drugs'. A careful review of the specification indicates that when only phosphatidylcholine is used in the formation of a vesicle, applicant uses NSAID as such and not a salt (Examples 8-17 with PC and diclofenac; Examples 18-25 with PC and ibuprofen). Rest of the examples uses a surfactant in addition. Thus the combination of 'consisting essentially of' as applied to salts of NSAIDs is deemed to be new matter.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Examples 18-25 disclose vesicles consisting essentially of, inter

alia, a sodium salt of ibuprofen rather than ibuprofen (acid form) as the Office asserts. According to applicant, Examples 18-25 state: "The preparation is as described in Examples 1 to 4, with the exception that, after the mixture is suspended, the pH is adjusted to a value of 7 by the addition of 10 M NaOH." (Specification, p. 37, lines 8-10 (emphasis added)) and that the addition of NaOH converts the ibuprofen (acid form) into its sodium salt. Accordingly, Examples 18-25 describe vesicles consisting essentially of, inter alia, containing ibuprofen sodium salt. This argument is not persuasive. First of all, the pH of the solution is 7 which means neutral and one would expect equilibrium between the salt and the acid (sodium ions and hydrogen ions) which means there is acid present too and not just the salt. There is no evidence presented to show that at this pH all of ibuprofen is in salt form. Secondly, claims are drawn to 'one or more non-steroidal anti-inflammatory drugs' which term encompasses numerous compounds and there is no evidence that at pH 7 all of these compounds are present only in salt form. Therefore, the rejection is maintained.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 124 and 129-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by "wherein a ***buffer an aqueous*** medium" in iv of claim 124.

Claim Rejections - 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 106, 112-115, 118 and 120-124 and 129-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vyas (Journal o micro encapsulation, 1995) or Hayward (5,585,109) or Sheffield (4,937,254) in combination r Radhakrishnan (5,043,165), Edger (5,498,420) by themselves or together in further combination with Mezei (4,897,269).

Vyas discloses topical application of liposomes consisting essentially of PC and diclofenac in PBS, pH 7.4 (abstract, Table 1 formulation L1).

Hayward discloses liposomal formulations containing soy lecithin and salicylic acid and a method of delivery to the skin. The carrier material is polymethacrylate gel. The pH is 6.5 to 7.5. The composition further contains antioxidants and preservatives and hydrocolloids (columns 3-7). What is lacking in Hayward is the use of claimed antioxidants and Stabilizers.

Sheffield teaches a method of topical administration of liposomal formulations containing phosphatidylcholine and NSAID. The method of administration is topically and either internally or externally which implies skin. The composition further contains PBS and hydrocolloids (col. 3, lines 7-56; col. 6, line 15 through col. 7, line 12, Examples 13-15).

What is lacking in Vyas, Hayward or Sheffield is the inclusion of benzyl alcohol. Vyas and Sheffield also do not teach the use of unilamellar vesicles of instant sizes. Hayward is silent with respect to the nature of the liposomes.

Radhakrishnan while disclosing liposomal formulations teaches that multilamellar preparations can be treated to produce small unilamellar vesicles, large unilamellar vesicles or oligolamellar vesicles which are characterized by sizes in the 0.04-0.08 microns, 0.1 to 0.5 microns and mixed micron range. Radhakrishnan further teaches that the advantage of the suvs is the greater packing density of the liposomes at a mucosal surface and suvs are preferred for topical or nasal use (col. 7, line 45 through col. 8, line 14).

Edger while disclosing liposomal formulations for topical use teaches that from statistical point of view the interaction of small unilamellar vesicles with other cells is

likely to be greater than that of multilamellar vesicles which facilitates the transfer of membrane constituents (col. 1, line 48 through col. 2, line 10).

Mezei while disclosing liposomal compositions teaches the addition of preservatives and antioxidants such as benzyl alcohol and tocopherol (abstract, Example 4 and col. 14, lines 42-63).

The use of small unilamellar vesicles of claimed sizes would have been obvious to one of ordinary skill in the art because of the advantages taught by Radhakrishnan and Edger. The addition of antioxidants and stabilizers in the compositions of Vyas or Hayward or Sheffield would have been obvious to one of ordinary skill in the art since such an addition would prevent oxidation of lipids and degradation by bacteria respectively as taught by Mezei. What is lacking in Hayward is the teaching of the use of synthetic phospholipid. However, since liposomes can be formed with either natural or synthetic phospholipids, it is deemed obvious to one of ordinary skill in the art to choose the desired source with a reasonable expectation of success. Hayward and Sheffield also lack the teaching of the application of the claimed amount of the liposomes on the skin surface. However, since the amount applied depends upon the condition to be treated and the severity of the condition, it is deemed obvious to one of ordinary skill in the art to manipulate this parameter to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Vyas does not teach or suggest either the recited at least one antioxidants or recited vesicle that is capable of penetrating through a permeability barrier having at least one constriction, wherein the vesicle is larger than

the constriction by more than a factor of 2 and less than a factor of 4. Applicant further argues that Vyas does not teach or suggest the recited vesicular compositions consisting essentially of a vesicle and a buffer. According to applicant, “In stark contrast, Vyas’s compositions comprise an oil-in-water emulsion, rather than a buffer solution. penultimate paragraph) • Further, Vyas does not provide any expectation whatsoever that replacing its oil-in-water emulsion with a buffer recited in the present claims would have successfully provided vesicles capable of transporting an NSAID through intact human or animal skin or mucous membranes and penetrating through a permeability barrier having at least one constriction, and the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4. Indeed, the Federal Circuit has recently held that identifying a reasonable expectation of success is crucial in "unpredictable" arts, such as chemistry, because "[t]o the extent an art is unpredictable, as the chemical arts often are. •. potential solutions are less likely to be genuinely predictable•" Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008)”.

These arguments are not persuasive. A careful review of the specification indicates that even in instant invention, consistency modifiers such as a hydrogel can be added (see also claims 116-117 dated 2-28-09). In essence, this implies other things can be added and Vyas uses an ointment base for topical application and since the liposomes of Vyas consists essentially of PC and diclofenac, it would have been obvious to one of ordinary skill in the art that they would behave the same way as in instant invention. Contrary to applicant’s arguments, Vyas uses phosphate buffer of pH

7.4 in the preparation of liposomes. With regard to instant limitation of permeability factor between 2 and 4, the examiner points out that Radhakrishnan teaches the advantage of suvs is the greater packing density of the liposomes at a mucosal surface and suvs are preferred for topical or nasal use; instant claims recites mucosal membranes. Edger also teaches the advantages of smaller vesicles. With regard to antioxidants, Mezei teaches both benzyl alcohol and tocopherol. Applicant argues that Sheffield does not teach or suggest administration of a vesicle to a human or animal skin that is intact. According to applicant, Sheffield teaches away from such an administration by emphasizing the delivery of its disclosed liposomes to a site of surgical trauma on the skin and point out to col. 3 of Sheffield. This argument is not persuasive since on col. 3, lines 39-41, Sheffield teaches "BY the term "topically", is meant that the NSAID is administered non-systemically to the surface of the tissue (internal or , in some cases external) to be treated". On col. 3, lines 51-53, Sheffield further defines the tissue as "Site of surgical trauma" also includes tissue that is adjacent to the injured tissue". This statement clearly indicates even intact skin is included. Applicant argues that Sheffield does not teach a vesicle that is capable of penetrating through a permeability barrier having at least one constriction, wherein the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4 and that he teaches multilamellar vesicles. These arguments are not persuasive since the rejection is made on the combination of references which include Radhakrishnan and Edger who teach the claimed sizes and the advantages. Applicant's arguments that Sheffield teaches away from the administration of vesicles that have size of 50 to 500

nm are not persuasive since the teachings of Sheffield on col. 6, lines 33-37 pertain to peritoneal cavity which means when the composition is administered internally and not topically on the skin. The examiner has already addressed applicant's arguments of Hayward's teaching away from the use of salts of NSAIDs in the previous action. In response to the examiner's position, applicant argues that pKa of most NSAIDs is between 3 and 5 as evident from Bosck et al, and based on the Henderson-Hasselback equation, an NSAID whose pKa=5 will be present in at least some salt from, if not predominantly in the salt form even at pH 3. This argument is not persuasive since 'most of NSAIDs' does not mean all of the NSAIDs behave the same way and all of them are weak acids. The reference submitted does not say anything about salicylic acid taught by Hayward. Furthermore, as applicants themselves previously stated that instant composition contains even NSAID not in a salt form. Applicant's arguments that Hayward states that the formation of salts of salicylic acid such as sodium salicylate formed by the combination of salicylic acid and sodium hydroxide, greatly improves the water solubility of the free acid, but substantially modifies the biological response to salicylic acid and as such one of ordinary skill in the art would understand that Hayward clearly teaches away from the use of a salt of a NSAID as presently claimed are not persuasive. If that were to be true, that is, the biological response is modified because of the salt formation, then one would expect similar behavior of the sodium salicylate even in instant invention since it is the inherent property of the compound. Instant specification provides no data at all on any NSAID let alone sodium salicylate.

Applicant argues that Mezei which teaches the addition of benzyl alcohol does not remedy the deficiencies of Vyas, Sheffield or Hayward and that even with benzyl alcohol added, the vesicles described by Vyas or Sheffield would still be larger than the claimed vesicle size. The rationale behind this argument is not readily apparent to the examiner since if that were to be true then it would even increase the sizes of instant liposomes, since it would be an inherent property of the compound. Furthermore, Mezei teaches tocopherols (antioxidants) besides benzyl alcohol.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is

(571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK